# Vitamin E and Evening Primrose Oil for Management of Cyclical Mastalgia: A Randomized Pilot Study

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Abstract

OBJECTIVE: To evaluate the effectiveness of vitamin E, evening primrose oil (EPO), and the combination of vitamin E and EPO for pain control in women with cyclical mastalgia. PROCEDURE: A double-blind, randomized, placebo-controlled trial was conducted at two U.S. academic medical centers. Eighty-five women with premenstrual cyclical breast discomfort were enrolled. Participants were randomly assigned to one of four six-month oral treatments: vitamin E (1,200 IU/day), EPO (3,000 mg/day), vitamin E (1,200 IU/day) plus EPO (3,000 mg/day), or double placebo. The primary outcome measure was change in breast pain, measured by the modified McGill Pain Questionnaire at enrollment and at six months. RESULTS: Forty-one patients completed the study. Intent-to-treat analysis (pretesting and post testing) showed a difference in worst-pain improvement with the treatments EPO ($p=0.005$), vitamin E ($p=0.04$), and EPO plus vitamin E ($p=0.05$), but no difference with placebo ($p=0.93$). Results from two-sample t-test showed a nonsignificant decrease in cyclical mastalgia individually for the three treatment groups compared with the placebo group (EPO, $p=0.18$; vitamin E, $p=0.10$; and EPO plus vitamin E, $p=0.16$). The data were also analyzed with the separation test by Aickin, which showed a trend toward a reduction of cyclical mastalgia with vitamin E and EPO individually and in combination. CONCLUSION: Daily doses of 1,200 IU vitamin E, 3,000 mg EPO, or vitamin E and EPO in combination at these same dosages taken for six months may decrease the severity of cyclical mastalgia. (*Altern Med Rev* 2010;15(1):59-67)

## Introduction

Cyclical mastalgia is a common condition in women seen in primary care practices.[1] The prevalence of mastalgia reported in the medical literature ranges from 4-69 percent.[2] The clinical presentation is often described as premenstrual breast pain and tenderness associated with swelling, regular occurrence during the luteal phase of the menstrual cycle, at least seven days duration, and resolution of symptoms with menstruation.

An estimated 70 percent of premenopausal women are affected by breast pain at some point in their life. For most women the symptoms are effectively managed with physician reassurance and conservative measures, such as use of a support bra or over-the-counter pain medication, including acetaminophen and nonsteroidal anti-inflammatory drugs.[1] When conservative measures are inadequate and pain is severe enough to interfere with occupational, social, or sexual activity, other drug options are considered, including danazol (attenuated androgen), tamoxifen citrate (selective estrogen-receptor modulator with estrogen agonist-antagonist properties), bromocriptine mesylate, luteinizing hormone-releasing hormone agonists, and progesterone/progestogens. Unfortunately, the short- and long-term adverse effects associated with some of these drugs preclude their use as first-line agents.[3]

Other therapies that may provide benefit include use of diuretics, abstinence from foods containing methylxanthines (e.g., coffee, chocolate, black tea), and vitamin $B_6$ supplementation.[1] Herbal and dietary supplements are often sought as alternative therapies by women with moderate-to-severe pain. Vitamin E and evening primrose oil (EPO) are examples of commonly used dietary supplements for management of cyclical mastalgia that have been evaluated in small studies.[4-6]

Vitamin E is the most commonly used vitamin for management of cyclical mastalgia. A potential mechanism of action is its role as an antioxidant,[7] although the extent of bioconversion of vitamin E to metabolites is unclear. Investigators suggest that

Key words: breast, essential fatty acids, evening primrose, menstrual cycle, vitamin E, mastalgia, PMS, GLA, tocopherol

the biological function and localization of vitamin E in membranes protects tissue against the harmful effects of free radicals generated during normal metabolic processes, such as steroid hormone synthesis.[8]

EPO is an essential fatty acid (EFA) used empirically by many women to reduce cyclical mastalgia. EPO is a rich source of EFAs and contains 7-14 percent gamma-linolenic acid (GLA). Its mechanism of action is thought to involve inhibition of prostaglandins that potentially contribute to breast pain. Dietary GLA is metabolized to dihomo-gamma-linolenic acid (DGLA), which can inhibit synthesis of arachidonic acid metabolites and exert an anti-inflammatory effect.[9] Investigators postulate that women with breast pain have low plasma levels of EFAs, including GLA and the immediate precursor of the prostaglandin $E_1$ series of prostanoids.[2,10] A deficiency of EFAs may cause hypersensitivity of breast epithelium to circulating hormones.[10] Dietary supplementation with GLA, as a rich source of EFAs, has been suggested to treat these deficiency syndromes.

## Objective

The authors hypothesized that the effects observed with vitamin E and EPO individually work synergistically and are more clinically effective in combination than individually. The objective was to study the effects of vitamin E and EPO alone and in combination for the treatment of cyclical mastalgia.

## Procedures

### Study Design

The study was randomized, double-blind, and placebo-controlled. Participants were assigned to receive for six months a placebo, vitamin E, EPO, or a combination of vitamin E and EPO Randomization was performed according to a random-number table. Participant allocation was masked to the researchers and conducted by a centralized pharmacy. Study design was approved by Mayo Clinic Institutional Review Board and the University of Minnesota Institutional Review Board and was registered on ClinicalTrials.gov (Unique Protocol ID 1957-02, NCT00275600).[11] Written informed consent was obtained from all participants, who received no remuneration for involvement in the trial. Participants were contacted monthly by telephone to assess compliance and adverse effects.

Participants were assigned to 400 IU vitamin E (one vitamin E capsule plus one placebo capsule) three times daily (n=21), 1,000 mg EPO (one EPO capsule plus one placebo capsule) three times daily (n=21), 400 IU vitamin E and 1,000 mg EPO (two capsules) three times daily (n=21), or placebo (two capsules) three times daily (n=22) for six months.

### Outcome Measure

The primary outcome measure was change in breast pain, measured by the modified McGill Pain Questionnaire at enrollment and at six months.

### Subjects

From March 1, 2003, through December 15, 2006, participants with cyclical breast pain were recruited from Mayo Clinic, in Rochester, Minnesota, and the University of Minnesota, Twin Cities. Eligibility criteria included premenopausal stage, age at least 18 years, and cyclical mastalgia, defined as pain that occurred within two weeks of menses onset, relieved by menses, and that had occurred during at least two consecutive menstrual cycles. Participants were eligible if they received no benefit from conservative measures (e.g., use of a support bra, physician reassurance) after one month. A score of 3 or greater on a breast-pain survey with pain scores from 1 to 10 (10 being worst pain) was also required. Participants age 40 years or older were required to have had a normal mammogram result and targeted ultrasound of the focal area of pain within the previous year. For participants younger than 40 years, the focal area of pain was evaluated by targeted ultrasound examination or a mammogram, or both, at the discretion of the patient's radiologist.

Ineligibility criteria included pregnancy or lactation; use of vitamin E (>200 IU/day) or EPO in the previous two weeks; regular use of aspirin, nonsteroidal anti-inflammatory drugs, or anticoagulant therapy; use of danazol, bromocriptine, or tamoxifen in the previous three months; and prior diagnosis of breast cancer. Use of a daily multivitamin supplement was not an exclusion criterion.

Participants made one clinic visit to determine eligibility and complete the consent process. Before enrollment, a baseline history of breast and gynecological health was obtained and a clinical breast examination was performed. The subjects were randomly assigned to a treatment protocol, which was packaged, labeled, and distributed by Mayo Clinic's research pharmacy.

**Table 1. Breast Pain Survey**

| |
|---|
| Is your breast pain related to your menstrual cycle? |
| How long have you had your breast pain? |
| What does your breast pain feel like? |
| In the past 30 days, how many days were you bothered by breast pain? |
| Describe the breast pain that occurs every month. |
| Indicate where the pain occurs. |
| Please rate your worst breast pain in the last month. |
| What was the average of your breast pain in the last month? |
| What kinds of things increase your breast pain? |
| Have you tried any over-the-counter products to help with breast pain? |
| How much has your breast pain limited you in the following activities?:<br>Work schedule<br>Sleep pattern<br>Sexual activity |
| Do you take prescription medications to relieve your breast pain? |
| Have you had a breast biopsy? |
| Have you had breast cancer? |
| Do you have other pains besides breast pain? |
| Have you had any other pains in the last 30 days for which you have sought treatment or taken additional medications? |
| Do you consume any caffeinated beverages or food (coffee, tea, soda pop, chocolate)? |
| Please include any comment not covered above. |

Data from Melzack[12] and Khan and Apkarian[13]

## Materials

Vitamin E, EPO, and placebo were obtained from New Health International, Inc., Tustin, California. Vitamin E was supplied as d-α-tocopherol (7.5 oval, clear; 400 IU) and mixed tocopherol (5 mg). The placebo vitamin E (7.5 oval, clear; corn oil, 389.5 mg) was designed to have an identical appearance to the vitamin E capsule. The EPO treatment contained 1,000 mg of EPO (20 oblong, clear; EPO, gelatin, glycerin, and purified water). The placebo EPO (20 oblong, clear; corn oil, 1,000 mg) was designed to have an identical appearance to the EPO capsule.

## Instruments

The short-form McGill Pain Questionnaire, a validated, widely used instrument for measurement of breast pain, was used.[12] This questionnaire addresses pain by using 15 descriptors that represent the sensory and affective dimension of the pain experience. Each descriptor is ranked on an intensity scale of 0 to 3. This form also includes both the "present pain intensity" entry of the standard long-form McGill Pain Questionnaire and the visual analogue scale to provide overall intensity scores. The questionnaire was modified further by Khan and Apkarian[13] to specifically address cyclical mastalgia. This questionnaire includes 15 questions that describe the breast pain, its relationship to the menstrual cycle, and what relieves and increases the breast pain; it also includes an anatomical drawing for participants to indicate the painful areas.

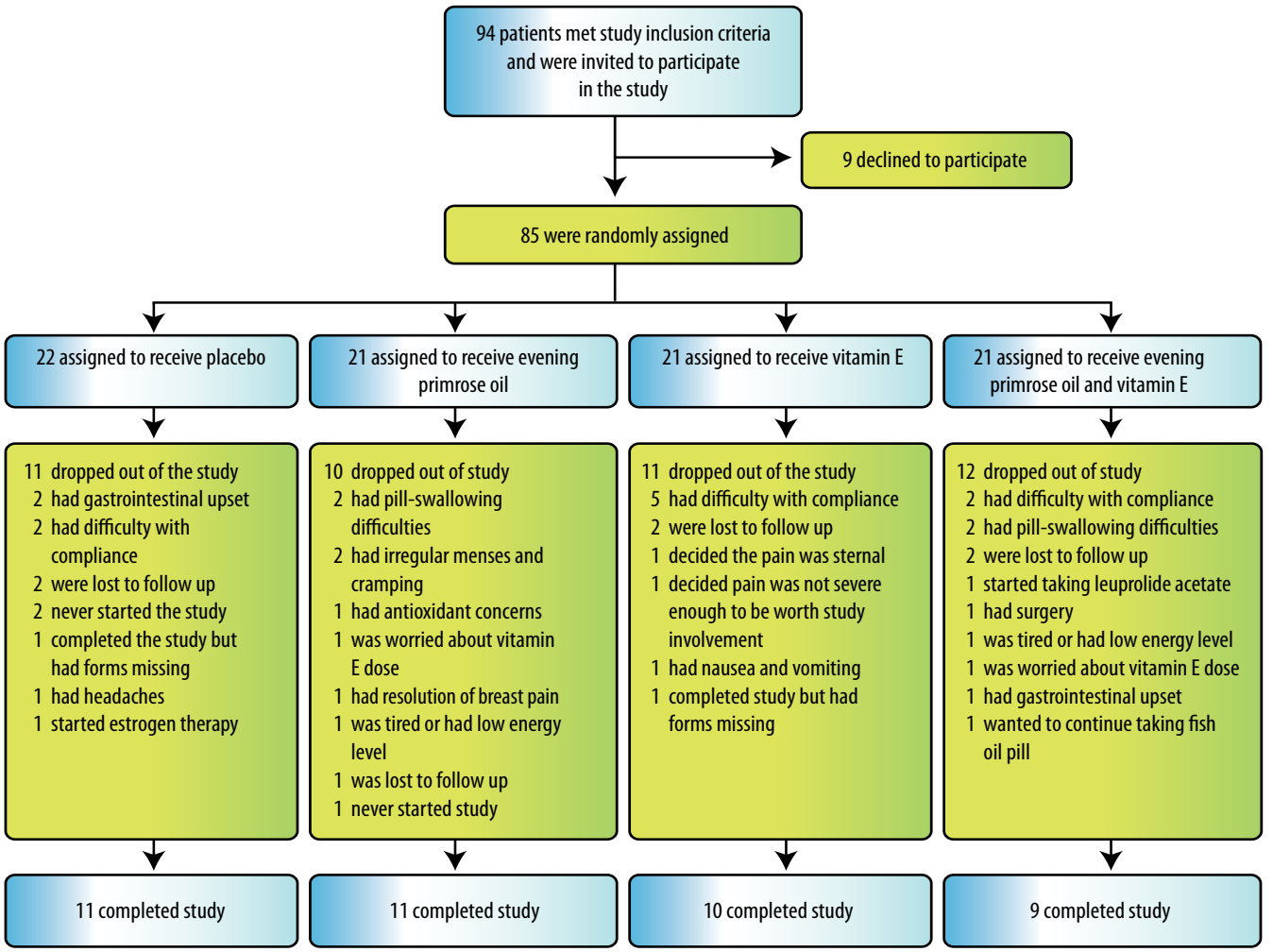
The questionnaire by Khan and Apkarian[13] was additionally modified and entitled "Breast Pain Survey" to specifically evaluate cyclical mastalgia (Table 1). Participants were asked to complete the Breast Pain Survey at baseline and after six months.

## Statistical Analysis

The baseline and six-month results and the differences between worst pain and average pain among the four groups were compared with one-way analysis of variance (ANOVA). Post hoc analysis of the pairwise comparisons was conducted using Dunnet's criteria. Comparisons of the differences in worst pain and average pain from baseline to six months in each treatment group were analyzed with the paired t-test. The analysis was performed using intent-to-treat and per-protocol approaches. Participants who did not complete either the six-month study period or the form were considered dropout participants; they were included in the intent-to-treat analysis, but were excluded in the per-protocol analysis.

With 20 participants in each group, a one-way ANOVA was used to detect an effect size of 0.1435 with a 0.05 two-sided significance level. It was calculated that, in using the Fisher protected least-squares difference test for the post hoc pairwise comparison, an effect size of 1.159 with a level at 0.008 could be detected. However, when the sample size decreased to 10 participants per group, the effect size doubled to 0.3039 for ANOVA, or 1.734 for pairwise comparison. The power of the study was too low to detect the originally planned effect size. Thus, using the separation test described by Aickin,[14] results could be reported as an early-phase study. The separation

Figure 1. Flow of Patients




test enabled assessment of the worth of future research on the effectiveness of the three treatment arms. With the separation test, the standard deviation effect (SDE) estimate of the mean difference was obtained and the value of Δ (1.645 SDE) calculated. If the mean difference (pain reduction in the treatment groups compared with pain reduction in the placebo group) exceeded Δ/2, further research would be recommended; if the mean difference was less than Δ/2 (in the unfavorable direction), then further research would not be recommended.

## Results

The flow of the clinical trial is diagrammed in Figure 1. The study group was composed of 85 patients – 73 from Mayo Clinic and 12 from the University of Minnesota – recruited from March 1, 2003, to December 15, 2006. Of the 94 invited participants, 41 completed the six-month study. There was no statistically significant difference in the dropout rate among the four groups. Figure 1 includes the reasons for participant dropout.

### Baseline Comparisons

The mean age of participants was 40.4 years (range, 19-56). Baseline characteristics, as well as the reported duration of breast pain and the number of days the participant was bothered by the pain, were similar in each of the four groups.

### Within-Group Analysis

The intent-to-treat analysis (pretesting and post testing) showed a statistically significant difference

Table 2. Comparison of Pain Scores from Within-Group and Between-Group Analyses[a]

| Variable | Group | | | | ANOVA p Value |
|---|---|---|---|---|---|
| | Placebo | EPO | Vitamin E | EPO+Vitamin E | |
| **Intent-to-Treat Analyses** | **(n=22)** | **(n=21)** | **(n=21)** | **(n=21)** | |
| Worst pain | | | | | |
| At baseline | 5.45 (2.11) | 6.81 (1.97) | 6.00 (2.00) | 6.29 (2.35) | 0.21 |
| At month 6 | 5.41 (1.74) | 5.95 (2.40) | 4.57 (2.73) | 5.14 (2.85) | 0.34 |
| Difference | -0.05 (2.46) | -0.86 (1.24) | -1.43 (2.96) | -1.14 (2.56) | 0.27 |
| Paired t test p value | 0.93 | 0.005 | 0.04 | 0.05 | |
| Average pain | | | | | |
| At baseline | 4.50 (1.92) | 5.29 (2.35) | 5.05 (2.18) | 4.29 (1.98) | 0.39 |
| At month 6 | 3.86 (1.25) | 4.24 (2.64) | 3.52 (2.52) | 3.57 (2.31) | 0.72 |
| Difference | -0.64 (1.59) | -1.05 (1.56) | -1.52 (2.86) | -0.71 (1.65) | 0.46 |
| Paired t test p value | 0.07 | 0.006 | 0.02 | 0.06 | |
| **Per-Protocol Analyses** | **(n=11)** | **(n=11)** | **(n=10)** | **(n=9)** | |
| Worst pain | | | | | |
| At baseline | 5.45 (2.81) | 6.55 (1.81) | 6.20 (2.39) | 5.89 (2.85) | 0.77 |
| At month 6 | 5.45 (2.25) | 4.91 (2.17) | 3.80 (2.97) | 3.22 (2.77) | 0.20 |
| Difference | 0.00 (3.55) | -1.64 (1.29) | -2.40 (3.72) | -2.67 (3.43) | 0.22 |
| Paired t test p value | 1.00 | 0.002 | 0.07 | 0.05 | |
| Average pain | | | | | |
| At baseline | 4.55 (2.50) | 4.91 (2.07) | 5.40 (2.76) | 3.78 (2.11) | 0.51 |
| At month 6 | 3.45 (1.29) | 2.91 (1.87) | 2.60 (2.72) | 2.11 (2.09) | 0.52 |
| Difference | -1.09 (2.12) | -2.00 (1.67) | -2.80 (3.61) | -1.67 (2.24) | 0.48 |
| Paired t test p value | 0.12 | 0.003 | 0.04 | 0.06 | |

Abbreviations: ANOVA = analysis of variance; EPO = evening primrose oil.
[a] Pain comparison analysis within each of the four study groups (paired t test) and between the four study groups (1-way ANOVA). Values are expressed as mean (SD) unless specified otherwise.

in worst-pain improvement for the three treatment arms (EPO, p=0.005; vitamin E, p=0.04; a borderline significant difference for EPO plus vitamin E, p=0.05) but not for the placebo arm (p=0.93) (Table 2).

### Between-Group Analysis

Results from one-way ANOVA showed the difference in the worst pain from baseline to six months among the four groups was not significant (p=0.27); the difference in the average pain among the four groups also was not significant (p=0.46) (Table 2). In addition, with the two-sample t-test (intent-to-treat analysis), there was a nonsignificant decrease in cyclical mastalgia individually for the three treatment groups compared with the placebo group (EPO, p=0.18; vitamin E, p=0.10; EPO plus vitamin E, p=0.16) (Figure 2).

### Per-Protocol Analysis

Results from the per-protocol analysis and the intent-to-treat analysis for the within-group and between-group analyses were not significant (Table 2).

### Separation Test

Results of the separation test showed a trend toward a benefit in reduction of cyclical mastalgia with vitamin E and EPO individually and in combination (Table 3).

**Figure 2. Improvement in Worst Pain Among Participants in the Four Study Arms**

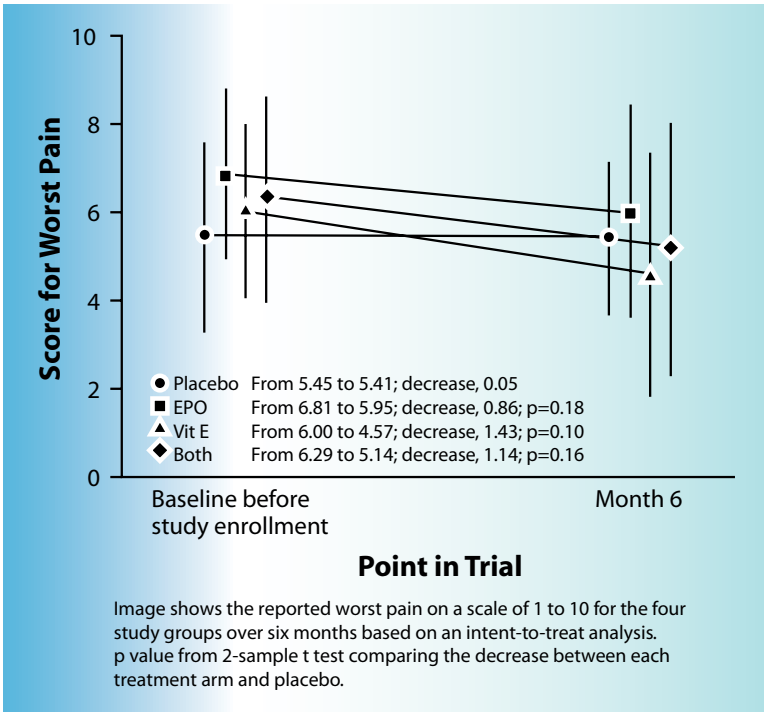



Image shows the reported worst pain on a scale of 1 to 10 for the four study groups over six months based on an intent-to-treat analysis. p value from 2-sample t test comparing the decrease between each treatment arm and placebo.

## Discussion

This pilot study with standard statistical analysis did not show a statistically significant decrease in cyclical mastalgia for the three treatment arms, which might be due to the study's small sample size. However, results of the separation test showed a trend toward a benefit with vitamin E and EPO, either individually or in combination. Results of the separation test support the need for a larger-scale study to evaluate the effectiveness of the three treatment arms in improving cyclical mastalgia.

Three small, randomized, double-blind, placebo-controlled studies have evaluated vitamin E supplementation as a potential treatment for breast pain.[5,8,15] These studies had a treatment duration ranging from 2-3 months and a vitamin E daily dose ranging from 15-600 IU. They showed no benefit of these regimens in the management of breast pain or benign breast disease. A more recent, four-month, randomized, double-blind, clinical trial of 150 premenopausal Iranian women assessed the therapeutic effects of 200 mg vitamin E twice daily or placebo for the treatment of cyclical mastalgia.[16] The study found that vitamin E had significant curative results at both two ($p<0.05$) and four months ($p<0.000$) in the case group versus the placebo group.

EPO has been evaluated in two small, randomized, double-blind, placebo-controlled studies of three-month duration.[4,17] The dosage of EPO was 3,000 mg/day in one study and not specified in the other. Both studies reported improvement in breast pain. Several sequential non-placebo-controlled studies and clinical trial series of EPO with dosages ranging from 2,000-3,000 mg/day and duration ranging from 2-6 months have shown favorable response in both cyclical and non-cyclical mastalgia.[12,18-20]

Another randomized, double-blind study evaluating EPO and fish oil in premenopausal women with severe cyclical or non-cyclical mastalgia showed no benefit from either EPO or fish oil over control oils.[21] In this study, women received two different oils, 3 g each. The capsule of EPO contained GLA (9.6%), linoleic acid (71.2%), and vitamin E (5 mg). The fish oil capsule contained eicosapentaenoic acid (37.6%), docosahexaenoic acid (23.8%), and vitamin E (1 mg). The corn oil capsule contained linoleic acid (60.3%) and served as a control for the fish oil (which also contained 60.3% linoleic acid). A combination of corn oil and

Table 3. Summary of Data Analysis for the Effectiveness of the Three Treatment Arms with Use of Separation Test[a]

| EPO Group Variable | Difference in Score (SD) | | | | |
|---|---|---|---|---|---|
| | Placebo (n=22) | EPO (n=21) | Δ/2[b] | Mean difference[c] | Indication |
| Days when bothered by pain | 0.05 (0.72) | -0.14 (0.79) | 0.09 | -0.19 | Improve |
| Worst pain last month | -0.05 (2.46) | -0.86 (1.24) | 0.25 | -0.81 | Improve |
| Average pain last month | -0.64 (1.59) | -1.05 (1.56) | 0.20 | -0.41 | Improve |
| Work schedule | 0.14 (0.36) | -0.10 (0.31) | 0.05 | -0.24 | Improve |
| Sleep pattern | 0.00 (0.31) | 0.05 (0.51) | 0.05 | 0.05 | NR |
| Sexual activity | -0.09 (0.29) | -0.05 (0.22) | 0.03 | 0.04 | Improve |
| Use of prescription drug | 0.05 (0.21) | 0.00 (0.00) | 0.02 | -0.05 | Improve |
| **Vitamin E Group Variable** | **Difference in Score (SD)** | | | | |
| | Placebo (n=22) | Vitamin E (n=21) | Δ/2[b] | Mean difference[c] | Indication |
| Days when bothered by pain | 0.05 (0.72) | -0.38 (1.02) | 0.11 | -0.43 | Improve |
| Worst pain last month | -0.05 (2.46) | -1.43 (2.96) | 0.35 | -1.38 | Improve |
| Average pain last month | -0.64 (1.59) | -1.52 (2.86) | 0.29 | -0.89 | Improve |
| Work schedule | 0.14 (0.36) | 0.00 (0.00) | 0.03 | -0.14 | Improve |
| Sleep pattern | 0.00 (0.31) | 0.00 (0.32) | 0.04 | 0.00 | NR |
| Sexual activity | -0.09 (0.29) | 0.05 (0.38) | 0.04 | 0.14 | Improve |
| Use of prescription drug | 0.05 (0.21) | 0.00 (0.00) | 0.02 | -0.05 | Improve |
| **EPO Plus Vitamin E Group Variable** | **Difference in Score (SD)** | | | | |
| | Placebo (n=22) | EPO+Vitamin E (n=21) | Δ/2[b] | Mean difference[c] | Indication |
| Days when bothered by pain | 0.05 (0.72) | -0.19 (0.75) | 0.09 | -0.24 | Improve |
| Worst pain last month | -0.05 (2.46) | -1.14 (2.56) | 0.32 | -1.10 | Improve |
| Average pain last month | -0.64 (1.59) | -0.71 (1.65) | 0.20 | -0.08 | Improve |
| Work schedule | 0.14 (0.36) | -0.05 (0.22) | 0.04 | -0.19 | Improve |
| Sleep pattern | 0.00 (0.31) | 0.05 (0.38) | 0.04 | 0.05 | Improve |
| Sexual activity | -0.09 (0.29) | 0.05 (0.38) | 0.04 | 0.14 | Improve |
| Use of prescription drug | 0.05 (0.21) | 0.00 (0.00) | 0.02 | -0.05 | Improve |

Abbreviations: EPO=evening primrose oil; NR=no recommendation

[a] as described by Aickin[14]

[b] Δ/2=1.645 x standard deviation effect/2

[c] If the mean difference (i.e., reduction in breast pain of treatment groups greater than of placebo group) exceeds Δ/2 in the favorable direction (negative for pain), further research would be recommended. If the mean difference is below -Δ/2 in the unfavorable direction (positive for pain), then further research would not be recommended.

wheat germ oil was used as the control for EPO (which contained 56.8% linoleic acid). Overall, the results of EPO trials are conflicting, citing variable effectiveness with variable daily dosing of 2,000-3,000 mg.

A study similar to the present trial was conducted in the United Kingdom by Goyal and Mansel,[22] who used a combination treatment arm of antioxidants and minerals (which included beta-carotene, vitamin C, vitamin $B_6$, zinc, niacin, and selenium in a coconut oil base) and essential fatty acids. The investigators found equivocal results in the reduction of breast pain symptoms. They compared placebo with one of four treatment groups using a parallel group design. The treatment groups were: (1) GLA and antioxidants, (2) placebo fatty acids and antioxidants, (3) GLA and placebo antioxidants, or (4) placebo fatty acids and placebo antioxidants for four menstrual cycles. The investigators reported a trend in breast pain improvement for all four treatment groups during the blinded treatment phase. In the open-treatment phase, however, breast pain improved in the placebo fatty acids group (which contained 500 mg of hydrogenated coconut oil and 10 mg of natural vitamin E), with a response rate of 40 percent. There was no significant difference among the four arms, indicating that the other arms did just as well. A recent meta-analysis by Srivastava et al,[23] restricted to randomized, controlled trials with EPO, showed ineffectiveness of EPO compared with placebo.

The added value of the present pilot study compared with prior studies is its evaluation of the higher range of dosing for EPO at 3,000 mg/day and vitamin E at 1,200 IU/day, along with a combination arm versus placebo in a randomized manner.

Although the present pilot study was conducted with a small sample size, it has been shown that pilot studies using the analysis format created by Aickin[14] are helpful in initially evaluating the potential benefit of complementary and alternative therapies. Because large randomized trials are expensive, pilot studies are important as an initial step in determining whether there is preliminary evidence to justify a larger, potentially costly study.

A limitation of the present study is that, of a total of 85 participants enrolled, only 41 participants completed the study. Dropout rate was high, but consistent, across the four groups. A possible reason for the low retention rate is the publication of a meta-analysis during the recruitment period that received negative media coverage about high-dose vitamin E supplementation being associated with increased all-cause mortality rates.[24] The mean age of participants in the 19 randomized controlled studies that met selection for the meta-analysis ranged from 47-84 years (a considerably greater age range than the present study). The vitamin E dose ranged from 16.5-2,000 IU/day.

Another limitation of the current study may have been the form of vitamin E used – d-α-tocopherol. Although α-tocopherol is the most common tocopherol found in dietary supplements, recent studies suggest other forms (e.g., γ-tocopherol) may have more potent anti-inflammatory effects.[25] Future studies should investigate other tocopherols or mixed tocopherols. Another consideration might be to use black currant seed oil (17% GLA) or borage oil (20-24% GLA), both richer sources of GLA than EPO (7-14% GLA).

## Conclusion

The findings from the present pilot study suggest that EPO, vitamin E, and EPO in combination with vitamin E may improve cyclical mastalgia. A larger, well-powered clinical trial may be indicated to further evaluate the effects of vitamin E and EPO on mastalgia. It is reasonable in a clinical setting to offer premenopausal women with severe cyclical mastalgia a short-duration trial with either vitamin E at a daily dose of 1,200 IU, EPO at a daily dose of 3,000 mg, or the combination of vitamin E and EPO in these same dosages.

## Acknowledgment

New Health International, Inc., provided the treatment products and placebo for this study, but did not participate in the study design or analysis of the results. Funding for this study was received from Mayo Clinic Complementary and Alternative Therapy Program and the Division of General Internal Medicine, Mayo Clinic, Rochester, Minnesota.

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